# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**022501Orig1s000**

# PHARMACOLOGY REVIEW(S)


**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

# PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

| | |
|---|---|
| NDA NUMBER: | 22-501 |
| SERIAL NUMBER: | 000 |
| DATE RECEIVED BY CENTER: | 3/26/09 |
| PRODUCT: | (b) (4) |
| INTENDED CLINICAL POPULATION: | Prevention of pregnancy |
| SPONSOR: | Warner Chilcott Company Inc. Fajardo, PR |
| DOCUMENTS REVIEWED: | Vol. 1.1 – 1.3 |
| REVIEW DIVISION: | Division of Reproductive and Urologic products (HFD- 580) |
| PHARM/TOX REVIEWER: | Krishan L. Raheja, D.V.M., Ph.D. |
| PHARM/TOX SUPERVISOR: | Lynnda Reid, Ph.D. |
| DIVISION DIRECTOR: | Scott Monroe, M.D. |
| PROJECT MANAGER: | Karl Stiller |

Date of review submission to Division File System (DFS): 6-15-09

## EXECUTIVE SUMMARY

### I. Recommendations

A. Recommendation on approvability: Pharmacology/toxicology data support approval of NDA 22-501 for [redacted] (b) (4) for contraception.

B. Recommendation for nonclinical studies: All pharmacology/toxicology data were reviewed under the sponsor's approved NDA 21-871 for Loestrin® 24 Fe (norethindrone acetate and ethinyl estradiol tablets, USP and ferrous fumarate tablets) for the contraception indication.

C. Recommendations on labeling: As required the Labeling is in accordance with PLR and provided in SPL format.

### II. Summary of nonclinical findings:

A. Brief overview of nonclinical findings: There are no new nonclinical findings. The safety of norethindrone acetate and ethinyl estradiol at concentrations of 1.0 mg and 0.010 mg, respectively, have been established in previously conducted nonclinical and clinical studies.

B. Pharmacologic activity: Norethindrone acetate is a progestin and ethinyl estradiol an estrogen.

C. Nonclinical safety issues relevant to clinical use: None

# *2.6 PHARMACOLOGY/TOXICOLOGY REVIEW*

## 2.6.1 INTRODUCTION AND DRUG HISTORY

**NDA number**: 22-501
**Review number**: 1
**Sequence number/date/type of submission**: 000/3-25-09/original submission
**Information to sponsor**: Yes ( ) No ( *)
**Sponsor and/or agent**: Warner Chilcott Company Inc. Fajardo, Pueto Rico/
Warner Chilcott (US), LLC Rockaway, New Jersey

**Manufacturer for drug substance**: Norethindrone acetate and Ethinyl estradiol by (b) (4) (b) (4).

**Reviewer name**: Krishan L. Raheja, D.V.M., Ph.D.
**Division name**: Reproductive and Urologic Products
**HFD #**: 580
**Review completion date**: 5-5-09

**Drug**:

Trade name: (b) (4)
Generic name: Norethindrone acetate (NA) and ethinyl estradiol (EE)
(1 mg NA/10 ug EE, 10 ug EE) tablets
Code name: -
Chemical name, CAS registry number and molecular formula/molecular weight are provided in the following table:

| Drug | Chemical name | CAS Registry No. | Emperical formula | Molecular weight |
|---|---|---|---|---|
| Norethindrone acetate | 19-Norpregn-4-en-20-yn-3-one, 17-(acetyloxy)-, (17α) | 51-98-9 | $C_{22}H_{28}O_3$ | 340.46 |
| Ethinyl estradiol | 19-Norpregna-1,3,5(10)-trien-20-yne—3,17-diol, (17α)- | 57-63-6 | $C_{20}H_{24}O_2$ | 296.40 |

**Relevant INDs/NDAs/DMFs**: IND 73,510; NDA 21-871

**Drug class**: Norethindrone acetate, a progestin and Ethinyl estradiol, an estrogen

**Intended clinical population**: Prevention of pregnancy

**Clinical formulation**: Tablets

**Route of administration**: Oral

**Disclaimer**: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

**Data reliance**: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22-501 are owned by Warner Chilcott Company Inc. or are data for which Warner Chilcott Company Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 22-501 that Warner Chilcott, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Warner Chilcott, Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-501.

**Studies reviewed within this submission:** None. All pharmacology/toxicology studies were referenced to the sponsor's approved NDA 21-871 for Loestrin ® 24 (norethindrone acetate/ethinyl estradiol) tablets for contraception.

**Studies not reviewed within this submission**: none

## OVERALL CONCLUSIONS AND RECOMMENDATIONS

**Conclusions:** There are no safety concerns as the sponsor's product Loestrin® 24 has been previously approved for contraception under NDA 21-871. Both products have the same active ingredients. The amount of norethindrone acetate is 1 mg/tablet for both Loestrin® 24 and (b) (4) However, while the amount of ethinyl estradiol is 20 ug/tablet in the approved Loestrin® 24, it is reduced to 10 ug under NDA 22-501. The dosing regimen for both formulations consists of continuous dosing for 24 consecutive days followed by 4 days on placebo tablets containing 75 mg ferrous fumarate. The safety of inactive ingredients in (b) (4) is established by showing that the quantity of inactive ingredients used in the manufacture of tablets is below the maximum potency outlined in FDA's Inactive Ingredients Database or otherwise that the inactive ingredients are generally recognized as safe per 21 CFR regulations.

Unresolved toxicology issues (if any): None

Recommendations: Pharmacology /toxicology data support approval of NDA 22-501.

Suggested labeling: Suggested Labeling is in accord with PLR and provided in SPL format. Section No. 13 Nonclinical toxicology and 13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility were not included in the draft labeling, which is mandatory and needs to be included. Sponsor will need to provide recommended labeling consistent with other combined oral contraceptives.

APPEARS THIS WAY ON ORIGINAL

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/s/
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Krishan L. Raheja
6/16/2009 01:17:01 PM
PHARMACOLOGIST

Lynnda Reid
6/22/2009 01:37:18 PM
PHARMACOLOGIST

**45 Day NDA Meeting Checklist**
**Pharmacology/Toxicology**

**NDA Number: 22-501** **Date: 4-22-09**
**Drug Name:** (b) (4) **Reviewer:** Krishan L. Raheja
**Sponsor:** Warner Chilcott Company, Inc.

**Date CDER Received:** 3-26-09
**Filing Date: 5-25-09**
**User Fee Date:**
**Expected Date of Draft Review:**

**On initial overview of the Pharm/Tox portion of the NDA application**

| | ITEM | YES / NO | COMMENTS |
|---|---|---|---|
| 1) | On its face, is the Pharm/Tox section of the NDA organized in a manner to allow substantive review to begin? | Yes | In lieu of nonclinical P/T information, sponsor has made reference toWarner Chilcott NDA 21-871 for Loestrin® 24 Fe (norethindrone acetate and ethinyl estradiol tablets, USP and ferrous fumerate tablets) which is an approved oral contraceptive containing NA and EE. It is low dose contraceptive consisting of new dose with less EE and new regimen of the combination of NA and EE. |
| 2) | Is the Pharm/Tox section of the NDA indexed and paginated in a manner to allow substantive review to begin? | NA | |
| 3) | On its face, is the Pharm/Tox section of the NDA legible so that substantive review can being? Has the data been presented in an appropriate manner? | NA | |
| 4) | Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? | NA | |
| 5) | If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the Sponsor clearly defined the differences and submitted reviewable supportive data? | NA | |

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|---|---|---|---|
| 6) | Does the route of administration used in animal studies appear to be the same as the intended human exposure? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route? | NA | |
| 7) | Has the sponsor submitted a statement(s) that all the pivotal Pharm/Tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? | NA | |
| 8) | Has the sponsor submitted a statement(s) that the Pharm/Tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns? | NA | |
| 9) | Has the proposed draft labeling been submitted?<br><br>Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.57?<br><br>Is information available to express human dose multiples in either $mg/m^2$ or comparative serum/plasma AUC levels? | Yes<br><br>No<br><br>NA | No. 13 Nonclinical toxicology and 13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility which are not included in the draft label, need to be included or explained. |
| 10) | From a Pharm/Tox perspective, is this NDA fileable? If not, please state in item #11 below why it is not. | Yes | |
| 11) | Reasons for refusal to file: | | |

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/s/
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Krishan L. Raheja
4/30/2009 11:51:20 AM
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